different subcellular compartments. Upon exposure to soluble host factors, microbial products, or microbes, the PMN phenotype rapidly transforms; first ingesting the microbe and thereby sequestering it in the phagosome, and then recruiting and activating a variety of responses targeted to kill and degrade the trapped microbe. This presentation aims to discuss some of the mechanisms underlying specific features of the PMN response within the context of innate immune response to and resolution of infection. Concomitant with PMN activation, membrane-bound granule compartments fuse with the nascent phagosome, thereby delivering enzymes as well as antimicrobial peptides directly to the microbe. Concurrently, the NADPH oxidase is assembled and activated at the phagosome membrane, generating reactive oxygen species that directly and indirectly contribute to microbial killing and degradation. Collectively, these orchestrated responses of the PMN create an intraphagosomal environment inhospitable to the phagocytosed microbe. The mechanisms underlying the generation and antimicrobial action of several bioactive species will be highlighted, as will the specific synergies between soluble circulating proteins and PMN responses that collaborate to eradicate invading microbes. PMN contribute to host defense in ways other than those directly associated with phagocytosis, as they release IL-8 and other chemokines to recruit additional immune cells to the fray and to modulate the antimicrobial activities of resident cells at the site of infection. Lastly, PMN direct biochemical and cellular events that contribute to the subsequent resolution of the inflammatory response, an essential step in returning to a homeostatic, resting state.

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Community-Acquired MRSA: What in the World is Going on? (invited)

52.001

The Origin and Evolution of MRSA

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Since the identification of the first methicillin resistant *S. aureus* (MRSA) isolate in 1961, there is extensive literature on its successful spread in the nosocomial setting, its incremental rise in antibiotic resistance and more recently, its emergence as a community associated pathogen spreading in otherwise healthy populations. Extensive genotyping of *S. aureus*, including genome sequencing of six MRSA strains, and determining the organization of the staphylococcal chromosomal cassettes that harbor the methicillin resistance gene, mecA, have identified six major pandemic clones that have spread along epidemic waves, consistent with the historic outbreaks caused by penicillin resistant in the 1950s. The current epidemic strain, commonly referred to as USA300, has aggressively spread across the United States causing an inordinate number of skin and soft tissue infections in diverse healthy populations ranging from children to senior citizens. Comparative genomic sequencing of the molecular scars of an epidemic strain that is rapidly changing. This lecture will discuss *S. aureus* epidemic waves and the current emergence of community associated MRSA.

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52.002

Evasion of Innate Host Defense by *Staphylococcus aureus*

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Human polymorphonuclear leukocytes (PMNs or neutrophils) are essential to the innate immune response against invading microorganisms. Although most bacteria are killed readily by PMNs, pathogens such as *Staphylococcus aureus* have evolved multiple mechanisms to circumvent destruction by neutrophils and thereby cause human infections. Notably, prominent community-associated methicillin-resistant *S. aureus* (CA-MRSA) strains have enhanced ability to evade killing by human PMNs and rapidly destroy these critical innate immune cells. CA-MRSA immune evasion is multifactorial and includes resistance to antimicrobial peptides, detoxification of neutrophil reactive oxygen species, production of cytolytic molecules, and reprogramming of normal neutrophil apoptosis or turnover. Collectively, the current data indicate enhanced CA-MRSA virulence is linked to evasion of killing by neutrophils, which likely underlies (at least in part) the ability of prominent CA-MRSA strains to cause disease in individuals without known risk factors for infection.

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52.003

Microbial Pathogenesis of Community-Acquired MRSA Infections

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Staphylococcus aureus is a commensal of the anterior nares. It permanently colonizes the moist squamous epithelium of about 20% of the population and intermittently colonizes another 60%. Several different bacterial surface proteins promote adhesion to desquamated nasal epithelial cells. Clumping factor B and iron-regulated surface determinant IsdA have been shown to stimulate efficient colonization of the nares of rodents, and in the case of ClfB, humans. ClfB binds to host cytokeratin 10 which is exposed on the surface of desquamated epithelial cells. When *S.aureus* breeches the skin it can cause both localized and invasive infections. The bacterium can express a plethora of surface-located and secreted molecules that promote infection. Surface proteins promote adhesion of bacteria to host cells and tissues. Surface polysaccharides and proteins help the bacterium to evade innate immune responses by inhibiting phagocytosis by neutrophils. The organism secretes proteins that can intefere with neutrophil migration and with complement